REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Invasive Candidiasis

Bart Jan Kullberg, M.D., Ph.D., and Maiken C. Arendrup, M.D., Ph.D.

Invasive candidiasis is the most common fungal disease among hospitalized patients in the developed world. Invasive candidiasis comprises both candidemia and deep-seated tissue candidiasis. Candidemia is generally viewed as the more common type of the disease, and it accounts for the majority of cases included in clinical trials. Deep-seated candidiasis arises from either hematogenous dissemination or direct inoculation of candida species to a sterile site, such as the peritoneal cavity (Fig. 1). Mortality among patients with invasive candidiasis is as high as 40%, even when patients receive antifungal therapy. In addition, the global shift in favor of nonalbicans candida species is troubling, as is the emerging resistance to antifungal drugs. During the past few years, new insights have substantially changed diagnostic and therapeutic strategies.

From the Department of Medicine and Radboudumc Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands (B.J.K.); and the Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen (M.C.A.). Address correspondence to Dr. Kullberg at the Department of Medicine, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands, or at bj.kullberg@radboudumc.nl.

N Engl J Med 2015;373:1445-56.
DOI: 10.1056/NEJMra1315399

EPIDEMIOLOGY

According to conservative estimates, invasive candidiasis affects more than 250,000 people worldwide every year and is the cause of more than 50,000 deaths. Incidence rates of candidemia have been reported to be between 2 and 14 cases per 100,000 persons in population-based studies.[1,2] Candidemia has often been cited as the fourth most common bloodstream infection.[3] Although this statistic applies to intensive care units (ICUs), in most population-based studies candidemia is reported as the seventh to tenth most common bloodstream infection. Incidence rates have been increasing or stable in most regions, although declining rates have been reported in high-incidence areas after improvements in hygiene and disease management were introduced.[2,4,5]

The incidence of candidemia is age-specific, with the maximum rates observed at the extremes of age. Risk factors are summarized in Table 1.[2,6,7] The presence of central vascular catheters, recent surgery (particularly abdominal surgery with anastomotic leakages), and the administration of broad-spectrum antibiotic therapy constitute the major risk factors for invasive candidiasis. Although candidemia has been described as the most common manifestation of invasive candidiasis, blood-culture–negative forms include syndromes such as chronic disseminated (hepatosplenic) candidiasis in patients with hematologic cancers and deep-seated infection of other organs or sites, such as the bones, muscles, joints, eyes, or central nervous system. Infections at most of these sites arise from an earlier or undiagnosed bloodstream infection. Conversely, the direct introduction of candida may occur at a sterile site, resulting, for example, in ascending renal candidiasis or candida peritonitis after intestinal surgery.[8] Deep-seated infections may remain localized or lead to secondary candidemia. The limited published data available suggest that invasive abdominal candidiasis may be much more common than recognized.[8,9]

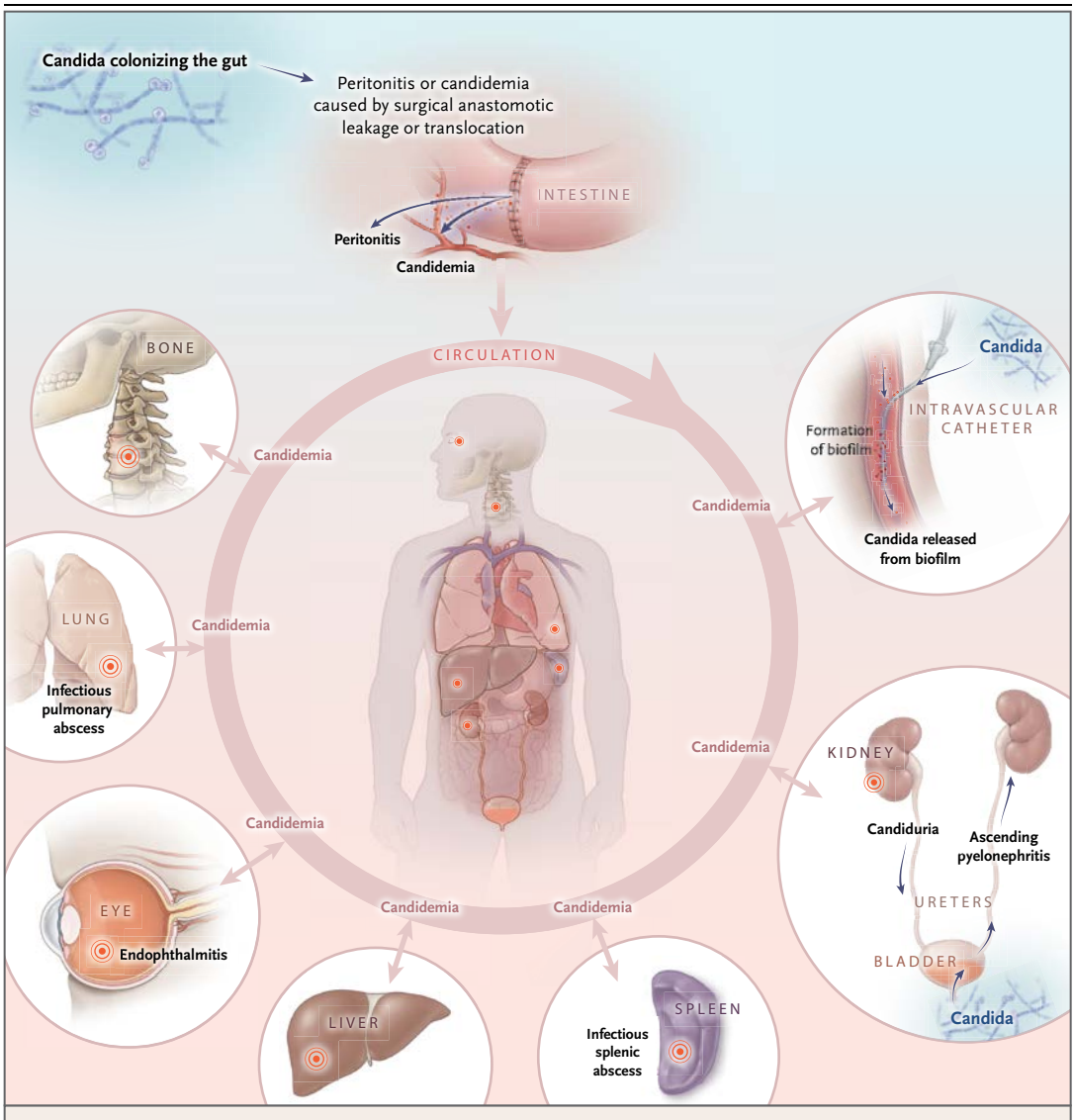

Figure 1. Pathogenesis of Invasive Candidiasis.

Candida species that colonize the gut invade through translocation or through anastomotic leakage after laparotomy and cause either localized, deep-seated infection (e.g., peritonitis), or candidemia. In patients with indwelling intravascular catheters, candidemia that originates from the gut or the skin leads to colonization of the catheter and the formation of biofilm. Fungi are subsequently released from the biofilm, causing persistent candidemia. Once candidemia has developed, whether from a colonized intravascular catheter or by other means, the fungi may disseminate, leading to secondary, metastatic infections in the lung, liver, spleen, kidneys, bone, or eye. These deep-seated infections may remain localized or lead to secondary candidemia. During candidemia, the fungi in the bloodstream may enter the urine, leading to candiduria. Less frequently, deep-seated candidiasis may occur as a result of ascending pyelonephritis and may either remain localized or lead to secondary candidemia.

CANDIDA SPECIES

The species distribution has changed over the past decades. Whereas *Candida albicans* had previously been the dominating pathogen, this species today accounts for only half the isolates detected in many surveys.[1,2,10] *C. glabrata* has emerged as an important pathogen in northern Europe, the United States, and Canada, whereas *C. parapsilosis* is more prominent in southern Europe, Asia, and South America. Changes in species distribution may drive treatment recommendations, given the

Table 1. Risk Factors for Invasive Candidiasis.*

Critical illness, with particular risk among patients with long-term ICU stay
Abdominal surgery, with particular risk among patients who have anastomotic leakage or have had repeat laparotomies
Acute necrotizing pancreatitis
Hematologic malignant disease
Solid-organ transplantation
Solid-organ tumors
Neonates, particularly those with low birth weight, and preterm infants
Use of broad-spectrum antibiotics
Presence of central vascular catheter, total parenteral nutrition
Hemodialysis
Glucocorticoid use or chemotherapy for cancer
Candida colonization, particularly if multifocal (colonization index >0.5 or corrected colonization index >0.4)

* ICU denotes intensive care unit. For further information see Cleveland et al.,[2] Arendrup et al.,[6] and Lortholary et al.[7]

differences in susceptibility to azoles and echinocandins among these species.

Candida species differ considerably in virulence. *C. parapsilosis* and *C. krusei* are less virulent than *C. albicans*, *C. tropicalis*, and *C. glabrata*.[11] This variation is reflected in the low mortality among patients with *C. parapsilosis* candidemia and in the fact that infection with *C. krusei* is highly uncommon except in patients with severe immunodeficiency and prior exposure to an azole.[6] Despite its low virulence, *C. parapsilosis* can thrive in certain clinical settings owing to its ability to adhere to medical devices and its propensity to colonize human skin, characteristics that facilitate nosocomial outbreaks.[12] Other species that appear with less frequency in clinical settings, such as *C. dubliniensis*, *C. lusitaniae*, *C. kefyr*, and *C. guilliermondii*, are associated with specific susceptibility patterns or with specific hosts (e.g., *C. dubliniensis* has been particularly common in HIV-infected patients).

IMMUNOGENETICS OF CANDIDA INFECTIONS

The majority of patients in the ICU do not acquire invasive candidiasis, even if they share similar risk factors. Thus, it is likely that variation in the genes that confer susceptibility to candida infection makes certain patients more prone to infection. A large clinical study revealed that susceptibility to candidemia was increased among European and North American patients who had single-nucleotide polymorphisms (SNPs) in the toll-like receptor 1–interferon-γ pathway, as compared with a clinical control cohort matched for underlying disease.[13] In a genomewide association study in which susceptibility to candidemia was assessed, three new genes associated with an increased risk of disease were identified. Patients in the ICU who carried two or more alleles at these particular loci had a risk of candidemia that was 19 times as high as the risk among patients who did not have those alleles.[14] Similarly, disease progression and persistent candidemia despite antifungal therapy were associated with cytokine polymorphisms that led to either increased circulating levels of antiinflammatory interleukin-10 or decreased levels of proinflammatory interleukin-12b cytokine.[15] These findings underscore the importance of cytokine balance with respect to both the susceptibility to acquiring invasive candidiasis and the ability to clear the infection once it has been disseminated. The identification of specific alleles related to the risk of disease and of cytokine pathways associated with unfavorable outcomes suggests that screening strategies based on the presence or absence of certain SNPs may help to identify patients at risk who could benefit from prophylactic antifungal treatment or adjunctive immunotherapy.[16]

DIAGNOSIS

The armamentarium available for diagnosing invasive candidiasis includes direct detection, in which specimens of blood or tissue from normally

sterile sites are cultured, and indirect detection, in which surrogate markers and polymerase-chain-reaction (PCR) assays are used (Table 2).[18,21,22] No test is perfect, and it is therefore necessary to perform several diagnostic tests to achieve maximal accuracy.

Culture is currently the only diagnostic approach that allows subsequent susceptibility testing. The sensitivity of blood cultures is far from ideal, with a sensitivity of 21 to 71% reported in autopsy studies.[9] Whereas blood cultures may establish a diagnosis during the period when candida resides in the bloodstream, cultures of blood obtained from patients with hematogenous, deep-seated infections often yield negative results because candida has been cleared from the bloodstream at the time the blood sample is collected.[9] Blood cultures are further limited by slow turnaround times and by the fact that a positive result may be revealed only late in the course of disease. Positive blood cultures should prompt the immediate initiation of therapy and a search for metastatic foci.[18,31]

Candida mannan antigens and antimannan antibodies and β-D-glucan are the primary surrogate markers for invasive candidiasis.[18,21,22] The reported performance of assays for these markers varies somewhat according to case mix, the frequency of sampling, and the choice of comparator. Studies that include healthy controls or less severely ill patients may overestimate specificity, since there are many potential sources of contamination of β-D-glucan testing that can produce false positive results, and these are found more frequently in patients at high risk for invasive candidiasis (Table 2). The major diagnostic benefit of β-D-glucan is its negative predictive value for invasive candidiasis in environments in which the prevalence is low to moderate.

A number of in-house PCR tests for the detection of invasive candidiasis have been evaluated. However, limited validation and standardization have hindered their acceptance and implementation.[27] Nguyen et al. reported that an in-house PCR assay had a sensitivity of 89% for deep-seated candidiasis that was not detected on blood cultures.[28] Two commercial PCR tests have been marketed — the SeptiFast and the fully automated multiplex T2Candida Panel, which was released in 2015.[29,30] The T2Candida Panel has recently been tested in one clinical trial that produced promising results (Table 2).[30]

PROPHYLAXIS

In view of the high mortality associated with invasive candidiasis, prophylaxis for selected patients in the ICU who are at high risk for the disease would appear to be appropriate. Until now, the use of antifungal prophylaxis in patients in the ICU has received little support from clinical studies, except for its use in specific high-risk groups.[32] In patients who have had recent abdominal surgery and have recurrent gastrointestinal perforations or anastomotic leakage, fluconazole prophylaxis has been shown to be effective.[33] In other selected patient groups in the ICU, the results have been modest at best. Antifungal prophylaxis has generally shown trends toward reducing the incidence of candidemia by approximately 50%, but this strategy has not been shown to improve survival.[34,35] The major challenge is to select individual patients or subgroups that will benefit most from prophylaxis in order to limit the number needed to treat and to avoid the problem of selective pressure that leads to the emergence of resistance.

A recent randomized, placebo-controlled study used targeted caspofungin prophylaxis in patients in the ICU who were determined to be at high risk for invasive candidiasis with the use of a clinical prediction rule.[36] In this study, both serum β-D-glucan levels and cultures were used to define invasive candidiasis. Overall, there were no significant differences between the study groups in the incidence of candidemia, all-cause mortality, the use of antifungal drugs, or the length of stay. In these types of placebo-controlled studies, culture- and biomarker-based end points may be less appropriate, since they are likely to be biased in favor of the group receiving the study drug. At this time, antifungal prophylaxis should be limited to patients in whom it has proved to be beneficial: patients with gastrointestinal anastomotic leakage, patients undergoing transplantation of the pancreas or the small bowel, selected patients undergoing liver transplantation who are at high risk for candidiasis, and extremely low-birth-weight neonates in settings with a high incidence of neonatal candidiasis.

Table 2. Diagnostic Tests for Invasive Candidiasis.*

Test and Specimen Type	Sensitivity	Specificity	Findings from Studies	Comments
	%			
Culture (blood)	21–71	NA	Per-patient sensitivity (based on autopsy studies) may be underestimated since patients with positive antemortem blood cultures but with no evidence of organ infection on autopsy were not included[9,17]	Obtain daily blood cultures (total volume, 40–60 ml in 10-ml bottles for adults) and additional sets during febrile episodes; sensitivity can be increased by including a mycosis bottle.[18]
β-D (blood)	65–100	31–79	Performance depends on cutoff value and no. of positive samples required[19] Sensitivity is species-dependent: *C. krusei,* 100%, 3 cases; *C. tropicalis,* 91%, 11 cases; *C. albicans,* 83%, 36 cases; *C. glabrata,* 81%, 26 cases; *C. parapsilosis,* 72%, 18 cases[20]	Not specific for candida. Positive test result requires confirmation and identification of infecting organism (aspergillus, *Pneumocystis jirovecii* or candida).[18,21] Many potential sources for contamination: hemodialysis with cellulose membranes, human blood products (immunoglobulins or albumin), amoxicillin–clavulanate or piperacillin–tazobactam, severe bacterial infections, surgical sponges and gauzes containing glucan, and severe mucositis.[22-24] High negative predictive value in several studies with intermediate prevalence.[20] However, limited sensitivity in other studies suggests that negative predictive value may be insufficient in high-risk patients.[19,21,25] Candida mannan antigen and antimannan antibodies tests may be preferable for circumstances in which candida is main fungal pathogen and risk of false positive β-D-glucan test is high.[25,26]
Candida mannan antigen and antimannan antibodies (blood or CSF)	Per patient, 83 (IQR, 79–87); per sample, 62 (IQR, 55–68)	Per patient, 86 (IQR, 82–90); per sample, 96 (IQR, 94–98)	Sensitivity and specificity results were given per patient and per sample[22] Sensitivity is species-dependent and lower for *C. parapsilosis* and *C. krusei* (40–50%) than for *C. albicans, C. glabrata* and *C. tropicalis* (80–100%)[26]	Combined antigen–antibody test required for maximum sensitivity. Used to detect blood-culture negative hepatosplenic candidiasis and CNS candidiasis.[22]
PCR assay (blood)				
Noncommercial	82–98	87–98	Patients had candidemia or invasive candidiasis[27]; results based on meta-analysis of range of in-house multiplex PCR assays	PCR formats specific for detection of candida preferred since they are less prone to contamination by airborne fungi and fungal DNA. In general, sensitivities are similar to those of culture results for candidemia and better for deep-seated candidiasis, with shorter turnaround time. Lack of multicenter validation.[27] For deep-seated candidiasis, sensitivity and specificity higher than with β-D-glucan.[17,28]
SeptiFast	48–72	99	Results based on meta-analysis[29]	Detects *C. albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis,* and *Aspergillus fumigatus.* Labor-intensive. Risk of false positive results for aspergillus.
T2Candida Panel	91	94	Multicenter study among 1501 patients (6 of 1501 candidemic) and additional 250 spiked samples[30]†	Detects *C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis.* Appears promising but validation in higher-risk populations needed.

* CFS denotes cerebrospinal fluid, CNS central nervous system, ICU intensive care unit, IQR interquartile range, NA not available, and PCR polymerase chain reaction. For further information see Cleveland et al.,[2] Arendrup et al.,[6] and Lortholary et al.[7]

† A spiked sample is a negative sample to which candida has been added.

EARLY TREATMENT

Retrospective observational studies have suggested that early presumptive antifungal therapy (therapy based on symptoms or biomarkers) is associated with reduced mortality among patients with invasive candidiasis.[37] Support has been provided by recent multivariate analyses, which corrected for confounders that were likely to introduce bias in observational cohort studies. These analyses consistently identified the early use of appropriate antifungal therapy and control of the source of infection as major determinants of survival.[38-40] Thus, although it is plausible that early, presumptive treatment of patients with invasive candidiasis is beneficial, such strategies have not been validated by prospective studies.

More refined approaches include treatment that is driven by prediction rules based on clinical risk factors, the presence of candida colonization, and the results of screening for serum β-D-glucan,[25,41] but to date no such approach has been shown to reduce mortality or length of stay in prospective studies. In addition, published prediction rules are not generally applicable in regions or settings that are different from those in the study.[42,43]

The clinical usefulness of prediction rules is affected by the low prevalence of invasive candidiasis.[9,43] In typical ICU settings, where the pretest likelihood of candidiasis is 0.5 to 10%, both individual, non–culture-based tests and risk-factor–based rules, which have a specificity of 50 to 80%, will lead to a positive predictive value of merely 1 to 30%.[42] Rather than being seen as definitive diagnostic tools, prediction rules and nonculture-based tests might be best viewed as markers that aid in the assessment of the possibility that a patient has invasive candidiasis.[9]

CHOICE OF ANTIFUNGAL THERAPY

Three classes of antifungal drugs are available for the treatment of invasive candidiasis (Table 3), and each new antifungal drug has been compared with a preexisting standard regimen in randomized trials. However, these studies were powered for noninferiority, and prospective studies intended to assess the superiority of one antifungal class of drug over another and to identify the most effective antifungal treatment strategies are unavailable.

Early studies showed that fluconazole, voriconazole, and caspofungin were as effective as amphotericin B deoxycholate and were associated with significantly lower levels of toxic effects and of treatment discontinuation.[44,45,47] The results of such studies marked the end of the use of amphotericin B deoxycholate as a treatment option for invasive candidiasis, except in environments with limited resources.[31] Micafungin was shown to be as effective as caspofungin and liposomal amphotericin B in two subsequent comparative trials.[49,50]

A pivotal study compared the efficacy of anidulafungin with that of fluconazole.[48] Although the study had been designed to assess the noninferiority of anidulafungin, overall response rates were significantly higher with anidulafungin than with fluconazole (76% vs. 60%; P=0.01). The apparent superiority of anidulafungin over fluconazole was most distinct in patients infected with *C. albicans* (global response, 81% vs. 62%; P=0.02), even though the *C. albicans* was almost uniformly susceptible to fluconazole.[48] Inferior outcomes with fluconazole were also observed in patients with low scores (indicating less severe disease) on the Acute Physiology and Chronic Health Evaluation (APACHE II), which suggested that inferior outcomes with fluconazole were not related to severity of illness. Post hoc multivariate analyses have not indicated that the differences in outcome with each drug were related to other, confounding factors.[51] Nevertheless, the question of whether a single noninferiority trial can establish the superiority of echinocandins over azoles for the treatment of invasive candidiasis has remained controversial, and opinions among experts in mycology are divided.

More recent studies have provided reasonable support, but no formal proof, for the superiority of echinocandins as treatment for the majority of patients with invasive candidiasis. Most notable is the pooled analysis of patient-level data from seven randomized trials that assessed antifungal treatments.[38] With 30-day all-cause mortality used as an unequivocal end point, the most important finding was that randomization to an echinocandin was associated with better survival rates and greater clinical success than treatment with a triazole or amphotericin B. The improved outcomes were most evident among patients infected with *C. albicans* or *C. glabrata*. The benefit of echinocandin therapy was observed among pa-

Table 3. Characteristics of Randomized, Controlled Trials for Invasive Candidiasis.

Study Regimen	Comparator Regimen	Treatment Duration	Step-Down Regimen	Primary Outcome	Standardized Success Rate*	All-Cause Mortality	Study
Fluconazole, 400 mg/day	Amphotericin B, 0.5–0.6 mg/kg body weight/day	≥14 Days after last positive blood culture and resolution of clinical signs	Not allowed	Clinical and microbiologic success at last available study visit	Fluconazole, 70%; amphotericin B, 79% (P=0.22)	Fluconazole, 40%; amphotericin B, 33% (P=0.20)	Rex et al., 1994[44]
Caspofungin, 50 mg/day†	Amphotericin B, 0.6–0.7 mg/kg/day (0.7–1.0 mg/kg/day for patients with neutropenia)	≥14 Days after last positive culture	≥10 Days, oral fluconazole, 400 mg/day	Clinical and microbiologic success at end of intravenous therapy	Caspofungin, 73%; amphotericin B, 62% (P=0.09)	Caspofungin, 34%; amphotericin B, 30% (P=0.23)	Mora-Duarte et al., 2002[45]
Fluconazole, 800 mg/day, and amphotericin B, 0.6–0.7 mg/kg/day	Fluconazole, 800 mg/day	Amphotericin B component, 5–8 days; fluconazole, ≥14 days after last positive blood culture and resolution of clinical signs	>5 Days, oral fluconazole, 800 mg/day	Time to failure (death, alternative therapy, or withdrawal)	Fluconazole plus amphotericin B, 69%; fluconazole, 56% (P=0.04)‡	Fluconazole plus amphotericin B, 40%; fluconazole, 39% (P=0.89)	Rex et al., 2003[46]
Voriconazole, 3 mg/kg, twice daily†	Amphotericin B, 0.7–1.0 mg/kg/day followed by fluconazole, 400 mg/day†	≥14 Days after last positive culture	Voriconazole group, >3 days, oral voriconazole, 200 mg twice daily; amphotericin B and fluconazole group: >3 days, fluconazole, 400 mg/day	Clinical and microbiologic success at 12 wk after end of therapy	Voriconazole, 65%; amphotericin B and fluconazole, 71% (P=0.25)	Voriconazole, 36%; amphotericin B and fluconazole, 42% (P=0.23)	Kullberg et al., 2005[47]
Anidulafungin, 100 mg/day†	Fluconazole, 400 mg/day	≥14 Days after last positive culture and improvement of clinical signs	≥10 Days, oral fluconazole, 400 mg/day	Clinical and microbiologic success at end of intravenous therapy	Anidulafungin, 76%; fluconazole, 60% (P=0.01)	Anidulafungin, 23%; fluconazole, 31% (P=0.13)	Reboli et al., 2007[48]
Micafungin, 100 mg/day	Liposomal amphotericin B, 3 mg/kg/day	>14 Days	Not allowed	Clinical and microbiologic success at end of intravenous therapy, per-protocol subgroup	Micafungin, 74%; liposomal amphotericin B, 70% (P=0.27)	Micafungin, 40%; liposomal amphotericin B, 40% (P=0.94)	Kuse et al., 2007[49]
Micafungin, 100 or 150 mg/day	Caspofungin, 50 mg/day†	≥14 Days after last positive culture and resolution of clinical signs	≥10 Days, oral fluconazole, 400 mg/day	Clinical and microbiologic success at end of intravenous therapy	Micafungin, 100 mg/day, 76%; micafungin 150 mg/day 71%; caspofungin, 72% (P=0.36)	Micafungin, 100 mg/day, 29%; micafungin 150 mg/day, 33%; caspofungin, 26% (P=0.19)	Pappas et al., 2007[50]

* The standardized success rate was based on the modified intention-to-treat population for the last available study visit[44,46,47] or the end of intravenous therapy.[45,48-50]

† Maintenance doses for fluconazole, caspofungin, voriconazole, and anidulafungin are shown. The loading doses, administered on the first day of treatment, are as follows: fluconazole, 800 mg; caspofungin, 70 mg; voriconazole, 6 mg per kilogram of body weight, two doses; and anidulafungin, 200 mg.

‡ These data are from a secondary analysis. P=0.08 for the primary analysis, which was a Kaplan–Meier time-to-failure analysis.

tients with APACHE II scores in all but the highest quartiles, suggesting that the survival benefit associated with echinocandin treatment is not limited to the sickest patients.[38] In addition to treatment with an echinocandin antifungal agent, the removal of intravenous catheters was an independent determinant of improved survival.[38]

Several cohort studies in which multivariate models were used have consistently identified treatment with an echinocandin and catheter removal as the management strategies associated with better outcomes.[40,52] Additional data have provided reasonable support for the efficacy of echinocandins in patients in the ICU, patients with deep-seated candidiasis, and patients infected with species other than *C. albicans*.[53,54] The observation that success rates among patients infected with *C. parapsilosis* are as good as those among patients infected with other species should be regarded with some caution. *C. parapsilosis* is less susceptible to the echinocandins than other candida species at the cellular and enzyme level and tends to be associated with higher persistence and breakthrough rates among patients receiving an echinocandin.[45]

Clinical trials and hence treatment guidelines are biased toward patients with candidemia, since the infection is easier to recognize and the patients easier to enroll in clinical studies than patients with deep-seated candidiasis. In addition, the comparison of trials is hampered, since the studies have been conducted over an extended period during which many advances in care have been introduced. Despite these caveats, echinocandins are suggested to be associated with better outcomes than those with azoles regardless of the type of invasive candidiasis, APACHE II score, and candida species (except for *C. parapsilosis*), and it is hard to justify withholding these agents as the first choice for treatment.[55] Nevertheless, some experts believe that there is a subgroup of ambulatory, stable, low-risk patients for whom primary therapy with fluconazole is acceptable. Moreover, there are clinical scenarios in which triazoles may be preferred, such as in the treatment of meningitis, endophthalmitis, and urinary tract candidiasis (conditions in which echinocandins are limited by their pharmacokinetics) or in the treatment of patients who have previously been exposed to echinocandins for prolonged periods.

DURATION OF THERAPY AND STEP-DOWN CARE

Few data are available to support recommendations regarding the total duration of therapy or the step-down procedure from echinocandins to intravenous or oral azoles.[56] Since it is assumed that initial therapy with echinocandins is most effective in preventing death, the primary requirement for the transition to azoles should be the clinical stabilization of the patient rather than identification of the infecting species and its susceptibility to azoles only — with the probable exception of *C. parapsilosis* infection.

Recent phase 4 studies have incorporated a step-down strategy to an oral azole as early as 5 days after the start of intravenous treatment with an echinocandin, provided that the infecting candida species has been cleared from the bloodstream and is probably susceptible to azoles and that the patient's condition is clinically stable and the patient is capable of taking oral therapy.[54] The outcomes of a strategy of early step-down with respect to efficacy and survival were similar to those reported in previous studies in which a minimum of 10 days of parenteral echinocandin therapy were required.[54] However, the intent of these studies was not to compare the effects of early step-down therapy with prolonged echinocandin therapy in a randomized fashion, and the patients who underwent the transition to azoles were less severely ill than other patients.

CATHETER MANAGEMENT

The concept supporting removal of intravascular catheters in patients with candidemia is based on the identification of catheters as a major risk factor for candidemia, the presence of biofilms of candida species attached to catheters, and the observation that candidemia may persist until catheters have been removed. However, no blinded, randomized studies have been designed to determine the effect of catheter removal on outcomes and mortality. It is unlikely that such a study will ever be performed, and retrospective subgroup analyses have shown divergent outcomes.[38,57,58] Although a careful analysis could not identify a significant effect of early catheter removal within 24 or 48 hours after initiation of treatment,[57] other studies found that catheter

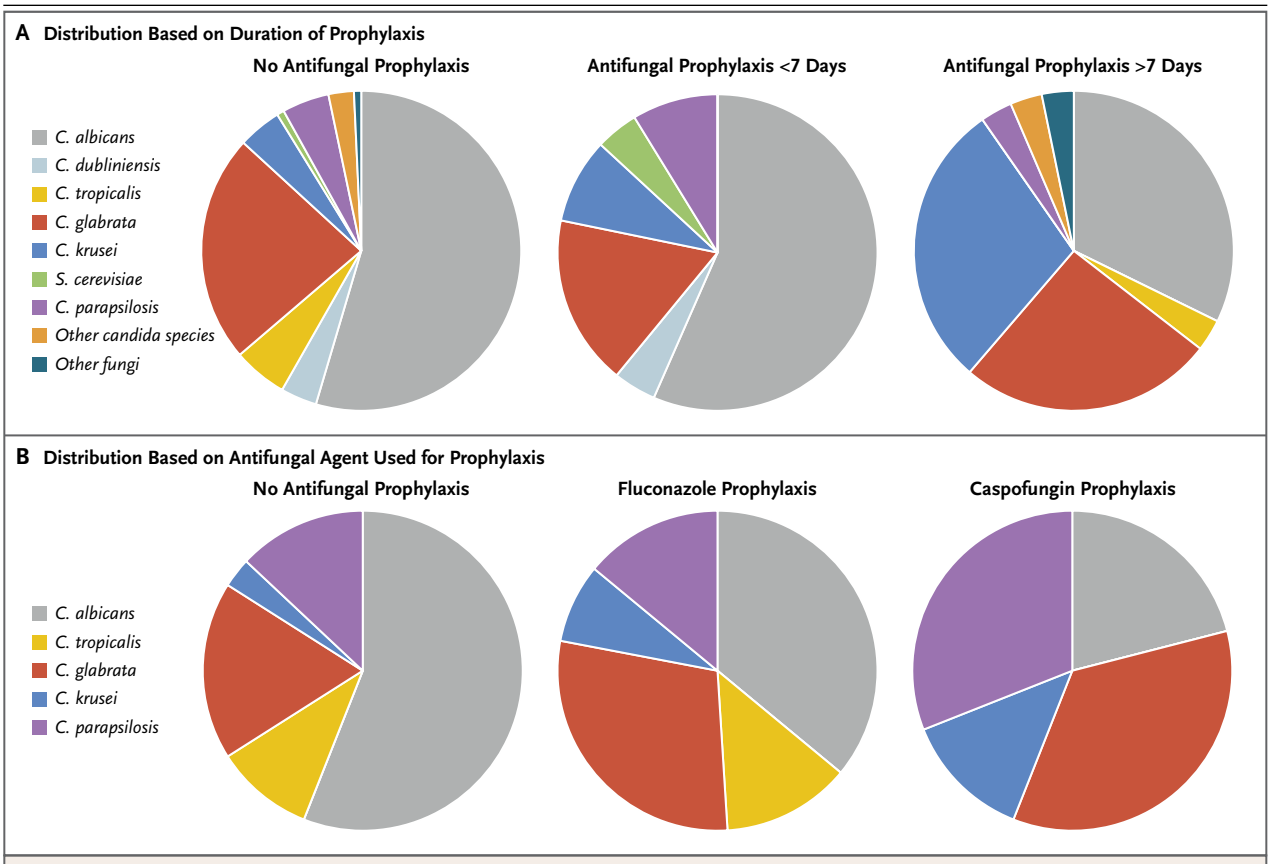

Figure 2. Distribution of Candida Species According to Duration of Prophylaxis and Antifungal Agent Used for Prophylaxis.

Panel A shows the distribution of candida species isolated from the bloodstream of patients with candidemia in a Danish study.[6] From left to right, the graphs show the distribution in patients who had received no antifungal prophylaxis at the time of blood culture (258 patients), those who had received antifungal prophylaxis for less than 7 days at the time of culture (21 patients), and those who had received antifungal prophylaxis for at least 7 days at the time of culture (28 patients) (P=0.007 according to the chi-square test). Antifungal prophylaxis included fluconazole in 37 patients (70%), voriconazole in 2 patients (4%), caspofungin in 6 patients (11%), and an amphotericin B formulation in 8 patients (15%) (some patients received more than one drug). Panel B shows the distribution of candida species isolated from the bloodstream of patients with candidemia in a French study.[60] From left to right, the graphs show the distribution in patients who had received no antifungal prophylaxis at the time of blood culture (2289 patients with no fluconazole exposure, and 2387 patients with no echinocandin exposure), those who had received fluconazole before the blood culture was performed (159 patients), and those who had received caspofungin before the blood culture was performed (61 patients).

removal at any time point was associated with a reduction in mortality and higher clinical success rates.[39,40,58] In the pooled patient-level analysis of seven randomized treatment trials, treatment with an echinocandin and catheter removal were identified as the two modifiable management strategies associated with better survival.[38] Because patients have to be alive to have a catheter removed, these types of analyses may not be free of bias. Although the debate about this issue will continue, it seems wise to remove all intravascular catheters in patients with candidemia, if logistically feasible.[31,55,59]

EMERGING RESISTANCE

Resistance to antifungal treatment can emerge either by means of the selection of species with intrinsic resistance or an induction of resistance in isolates from species that are normally susceptible. The former route is the most common, as illustrated by the emergence of *C. glabrata* after the introduction of fluconazole and of *C. parapsilosis* in settings in which there was increased use of echinocandins (Fig. 2).[6,60] In addition, insufficient dosing of azoles has been associated with the emergence of resistance.[61]

Candida isolates with acquired resistance to echinocandins have been reported with increasing frequency.[62] *C. glabrata* is overrepresented among echinocandin-resistant isolates, with resistance rates of 2 to 5% and up to 8 to 12% at selected centers for tertiary care.[62,63] Acquired resistance to echinocandins has also been reported for *C. albicans*, *C. tropicalis*, *C. krusei*, *C. kefyr*, *C. lusitaniae*, and *C. dubliniensis*.[62] Recent studies indicate that the rate of acquired resistance to echinocandins in isolates from sources other than blood may be underestimated, which suggests that deep-seated candidiasis may act as a hidden reservoir of echinocandin resistance.[64]

CONCLUSIONS AND FUTURE PERSPECTIVES

The management of invasive candidiasis has changed markedly during the past decade. Changes in epidemiology and the emergence of resistance, against both triazoles and echinocandins, merit vigilance. We have entered a new era in which better outcomes for patients with invasive candidiasis are less likely to result from new drugs than from early intervention strategies that are based on a combination of clinical prediction rules, non–culture-based tests (e.g., PCR assays or tests for antigens), and, ultimately, personalized, immunogenetics-based risk profiles. At present, the most important need is for studies that will validate the role of nonculture-based diagnostics in presumptive early treatment strategies.

Accumulating evidence points to the importance of early and appropriate antifungal treatment as a major driver of outcomes. Echinocandins appear to be the drugs of first choice for most patients, irrespective of the severity of illness. This development has marked a paradigm shift in the treatment of invasive candidiasis: treat early with an echinocandin and step down early to a triazole, giving consideration to the clinical stabilization of the patient, the candida species, and its susceptibility. By defining the most effective approach to the management of invasive candidiasis, we may finally begin to see declining mortality among patients with candidemia.

Dr. Kullberg reports receiving fees for serving on an advisory board from Cidara, lecture fees and travel support from Pfizer, and grant support from Astellas; and Dr. Arendrup, receiving fees for serving on advisory boards from Merck, lecture fees from Gilead, Merck, Pfizer, and Basilea, grant support through her institution from Gilead, fees paid to her institution from Gilead, Pfizer, Astellas, and Basilea for participation in the national surveillance fungemia program in Denmark, fees paid to her institution from Astellas for contract work, and fees paid to her institution from Basilea for microbiologic testing. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Arendrup MC. Epidemiology of invasive candidiasis. Curr Opin Crit Care 2010;16:445-52.
2. Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PLoS One 2015; 10(3):e0120452.
3. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-17.
4. Gradel KO, Schønheyder HC, Arpi M, Knudsen JD, Ostergaard C, Søgaard M. The Danish Collaborative Bacteraemia Network (DACOBAN) database. Clin Epidemiol 2014;6:301-8.
5. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198-208.
6. Arendrup MC, Sulim S, Holm A, et al. Diagnostic issues, clinical characteristics, and outcomes for patients with fungemia. J Clin Microbiol 2011;49:3300-8.
7. Lortholary O, Renaudat C, Sitbon K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002-2010). Intensive Care Med 2014;40:1303-12.
8. Leroy O, Gangneux J-P, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med 2009;37:1612-8.
9. Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 2013;56:1284-92.
10. Guinea J, Zaragoza Ó, Escribano P, et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. Antimicrob Agents Chemother 2014;58:1529-37.
11. Arendrup M, Horn T, Frimodt-Møller N. In vivo pathogenicity of eight medically relevant Candida species in an animal model. Infection 2002;30:286-91.
12. Vaz C, Sampaio P, Clemons KV, Huang Y-C, Stevens DA, Pais C. Microsatellite multilocus genotyping clarifies the relationship of Candida parapsilosis strains involved in a neonatal intensive care unit outbreak. Diagn Microbiol Infect Dis 2011;71:159-62.
13. Plantinga TS, Johnson MD, Scott WK, et al. Toll-like receptor 1 polymorphisms increase susceptibility to candidemia. J Infect Dis 2012;205:934-43.
14. Kumar V, Cheng S-C, Johnson MD, et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. Nat Commun 2014;5: 4675.
15. Johnson MD, Plantinga TS, van de Vosse E, et al. Cytokine gene polymorphisms and the outcome of invasive candidiasis: a prospective cohort study. Clin Infect Dis 2012;54:502-10.
16. Kullberg BJ, van de Veerdonk F, Netea MG. Immunotherapy: a potential adjunctive treatment for fungal infection. Curr Opin Infect Dis 2014;27:511-6.

17. Fortún J, Meije Y, Buitrago MJ, et al. Clinical validation of a multiplex real-time PCR assay for detection of invasive candidiasis in intensive care unit patients. J Antimicrob Chemother 2014;69:3134-41.
18. Cuenca-Estrella M, Verweij PE, Arendrup MC, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect 2012;18:Suppl 7: 9-18.
19. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis 2011;52:750-70.
20. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1 — >3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 2005;41:654-9.
21. Lamoth F, Cruciani M, Mengoli C, et al. β-Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). Clin Infect Dis 2012; 54:633-43.
22. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. Crit Care 2010;14:R222.
23. Poissy J, Sendid B, Damiens S, et al. Presence of Candida cell wall derived polysaccharides in the sera of intensive care unit patients: relation with candidaemia and Candida colonisation. Crit Care 2014;18:R135.
24. Sulahian A, Porcher R, Bergeron A, et al. Use and limits of (1-3)-β-d-glucan assay (Fungitell), compared to galactomannan determination (Platelia Aspergillus), for diagnosis of invasive aspergillosis. J Clin Microbiol 2014;52:2328-33.
25. Tissot F, Lamoth F, Hauser PM, et al. β-Glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. Am J Respir Crit Care Med 2013;188:1100-9.
26. Sendid B, Poirot JL, Tabouret M, et al. Combined detection of mannanaemia and antimannan antibodies as a strategy for the diagnosis of systemic infection caused by pathogenic Candida species. J Med Microbiol 2002;51:433-42.
27. Avni T, Leibovici L, Paul M. PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. J Clin Microbiol 2011;49:665-70.
28. Nguyen MH, Wissel MC, Shields RK, et al. Performance of Candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin Infect Dis 2012;54:1240-8.
29. Chang S-S, Hsieh W-H, Liu T-S, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis - a systemic review and meta-analysis. PLoS One 2013;8(5):e62323.
30. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis 2015;60:892-9.
31. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48:503-35.
32. Muldoon EG, Denning DW. Prophylactic echinocandin: is there a subgroup of intensive care unit patients who benefit? Clin Infect Dis 2014;58:1227-9.
33. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med 1999;27:1066-72.
34. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. Ann Surg 2001;233:542-8.
35. Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. Crit Care Med 2005;33: 1928-35.
36. Ostrosky-Zeichner L, Shoham S, Vazquez J, et al. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by pre-emptive therapy for invasive candidiasis in high-risk adults in the critical care setting. Clin Infect Dis 2014;58:1219-26.
37. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis 2006;43:25-31.
38. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54:1110-22.
39. Puig-Asensio M, Pemán J, Zaragoza R, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit Care Med 2014;42:1423-32.
40. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis 2012;54:1739-46.
41. León C, Ruiz-Santana S, Saavedra P, et al. Usefulness of the "Candida score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. Crit Care Med 2009;37:1624-33.
42. Bruyère R, Quenot JP, Prin S, et al. Empirical antifungal therapy with an echinocandin in critically-ill patients: prospective evaluation of a pragmatic Candida score-based strategy in one medical ICU. BMC Infect Dis 2014;14:385.
43. Playford EG, Lipman J, Kabir M, et al. Assessment of clinical risk predictive rules for invasive candidiasis in a prospective multicentre cohort of ICU patients. Intensive Care Med 2009;35:2141-5.
44. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 1994;331:1325-30.
45. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020-9.
46. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003;36:1221-8.
47. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435-42.
48. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007; 356:2472-82.
49. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519-27.
50. Pappas PG, Rotstein CMF, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45:883-93.
51. Reboli AC, Shorr AF, Rotstein C, et al. Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome. BMC Infect Dis 2011;11:261.
52. Eschenauer GA, Carver PL, Lin SW, et al. Fluconazole versus an echinocandin for Candida glabrata fungaemia: a retrospective cohort study. J Antimicrob Chemother 2013;68:922-6.
53. Ruhnke M, Paiva JA, Meersseman W, et al. Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients. Clin Microbiol Infect 2012;18:680-7.

54. Vazquez J, Reboli AC, Pappas PG, et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. BMC Infect Dis 2014;14:97.
55. Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18:Suppl 7:19-37.
56. Oude Lashof AML, Donnelly JP, Meis JFGM, van der Meer JWM, Kullberg BJ. Duration of antifungal treatment and development of delayed complications in patients with candidaemia. Eur J Clin Microbiol Infect Dis 2003;22:43-8.
57. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010;51:295-303.
58. Horn DL, Ostrosky-Zeichner L, Morris MI, et al. Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. Eur J Clin Microbiol Infect Dis 2010;29:223-9.
59. Brass EP, Edwards JE. Should the guidelines for management of central venous catheters in patients with candidemia be changed now? Clin Infect Dis 2010;51:304-6.
60. Lortholary O, Desnos-Ollivier M, Sitbon K, Fontanet A, Bretagne S, Dromer F. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. Antimicrob Agents Chemother 2011;55:532-8.
61. Shah DN, Yau R, Lasco TM, et al. Impact of prior inappropriate fluconazole dosing on isolation of fluconazole-nonsusceptible Candida species in hospitalized patients with candidemia. Antimicrob Agents Chemother 2012;56:3239-43.
62. Arendrup MC, Perlin DS. Echinocandin resistance: an emerging clinical problem? Curr Opin Infect Dis 2014;27:484-92.
63. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis 2013;56:1724-32.
64. Shields RK, Nguyen MH, Press EG, Clancy CJ. Abdominal candidiasis is a hidden reservoir of echinocandin resistance. Antimicrob Agents Chemother 2014;58:7601-5.